The appropriateness and risks of tablet splitting

M Sanetta Mosena, BPharm
Elsabé van der Merwe, BPharm, MSc (Pharmacology)

Abstract
Tablet division is applied where tablets of higher strength are split in half, or quarters, to provide the patient with a lower dose. The exercise is considered compounding by the pharmacist and is mostly used to make the titration of the required dose possible, as well as to save cost where tablets in a product range are flat-priced.

Studies showed that medication cost can be reduced substantially by implementing tablet splitting. Cost of tablet splitters and additional dispensing fees may however reduce savings somewhat, as may possible additional outpatient facility visits, especially in the initial few weeks after introducing tablet division to a medical scheme population.

Splitting scored tablets is approved by the FDA as efficacious and safe, but studies show that the half tablet weights of divided scored tablets often do not pass the dose content uniformity tests. Furthermore, in a recent study the drug content of half tablets, as determined by chemical assay, was not within the USP specifications for nearly 25% of products tested. In these studies, the physical characteristics like scoring and shape did not seem to predict which products would pass the uniformity test.

Certain types of tablets are generally not suitable for splitting, for example extended-release formulations and film or enteric-coated tablets, but there may be exceptions. Tablet size and shape may also play a role in the decision to split a tablet or not. Tablets containing drugs with a wide therapeutic index and long half-life may be more suitable candidates for division. Therefore, some tablets used for depression, hypertension and hyperlipidaemia may be considered for splitting, provided that product and patient characteristics are taken into account. Elderly patients, or those with impaired eyesight, cognition and/or dexterity may find it difficult to split tablets and take them correctly.

Tablet splitting carries a risk of errors due to misinterpretation of the prescription or label instructions by the pharmacist or patient, respectively. Nevertheless, where implemented carefully and with the appropriate counselling, tablet splitting does not compromise patient adherence and satisfaction or clinical outcomes negatively, and this was especially proven for statins.

Introduction
Tablet splitting is a practice where tablets of higher strength are broken in half, or quarters, to provide the patient with a lower dose. Tablet splitting facilitates the titration of the required dose for each patient. It also aids in the administration of larger tablets that patients may find hard to swallow whole.

The exercise of tablet splitting is considered compounding by the pharmacist, because the prescription is customised to give appropriate dosage and goes further than dispensing a commercially prepared product. Splitting scored tablets is approved by the FDA as efficacious and safe. It is not considered problematic if the lowest available strength on the market is divided to provide a specific dose for a patient who needs less drug. However, according to the FDA Modernization Act of 1997, Section 503A, the pharmacist can violate federal statute if a tablet is split to reproduce a dosage which is commercially available. There is no regulation in the South African Medicines and Related Substances Act (1965) pertaining to tablet splitting.

The other main reason for the practice of tablet splitting is to lower medication costs for patients and medical schemes. It was found that different strengths of the same medication may have the same price or have little cost difference. Therefore, when patients cannot afford their prescribed medication, they are often given a higher strength than is required with the aim to divide the tablet so that the cost can be reduced.
The American Medical Association and American Pharmacists Association (APhA) oppose mandatory tablet splitting as imposed by health insurers.10,11 Locally, the Pharmaceutical Society of South Africa (PSSA) also noted that some medical schemes may only approve payment if providers supply higher strengths in half the usual quantity of the originally prescribed product, but warns that the pharmacist must take professional responsibility for therapeutic failure if tablets unsuitable for splitting are provided with the intention to be split.12

In this article, the appropriateness and risks of tablet splitting are discussed. We will evaluate how cost of medication is minimised by the tablet splitting practice. Furthermore we will look at the ramifications that can compromise the stability and dosage of a particular medicine, thus rendering products unsuitable for splitting. On the other hand, certain tablets may well be suitable for splitting and we will investigate the characteristics of these.

The accuracy and success of dividing tablets, however, also depends on the technique and device used, as well as on patient and dispensing factors.5,6,11,13 Therefore, this article will identify the patients that should preferably be excluded from this practice and the possible errors that have to be taken into consideration when tablet splitting is implemented.

Cost containment
Tablet splitting is implemented as a strategy to save money for health insurers (medical aid schemes). The patients are expected to obtain the higher strength of a specific medication and break each tablet in half.4,6,11,12,14 For example, if a 20 mg tablet is prescribed, a 40 mg is approved by the scheme so that the patient takes half of the 40 mg; in this way the medication cost is approximately halved. The cost of medication can be significantly minimised by splitting flat-priced tablets, which is when the cost of different dosage strengths are equivalent.6,8,14,15

The Veterans Affairs Palo Alto Health Care System implemented a tablet splitting program to evaluate the cost savings with statin therapy. The tablets included in this study contained simvastatin, lovastatin or atorvastatin. These tablets were chosen because they:

• Were flat-priced in the US at the time of the study
• Accounted for high drug cost
• Were considered to have suitable pharmaceutical characteristics for tablet splitting

Patients with any cognitive or physical barriers were excluded from the study. The participants (n = 2019) were chosen using the computerised pharmacy prescription database. Prescription records of the statins over a one year period were used to determine the cost avoidance, which was calculated as follows: Cost avoidance per dose = Cost of full tablet - Cost of alternative half tablet (e.g. cost of simvastatin 20 mg tablet - half the cost of simvastatin 40 mg tablet). This was then multiplied by the total number of doses filled by all patients. The purchase costs of tablet splitters were subtracted. No additional staff was employed to educate patients on tablet splitting. In conclusion, it was found that the total cost avoidance over one year (October 2000 – September 2001) for simvastatin, lovastatin and atorvastatin was $138 108.14

Another study was conducted by Nebraska Medicaid to evaluate cost minimisation when patients take half a sertraline 100 mg to obtain the 50 mg dose. The 50 mg dose was selected because it is a frequently prescribed dose of sertraline and dividing the 100 mg previously reduced costs of sertraline in the hospital setting. The study was conducted to investigate whether mandatory tablet splitting would be an effective and appropriate way of containing ever-increasing drug cost in this Medicaid population.

Pharmacists were expected to pre-split tablets to ensure that they were split evenly and then inform patients regarding the half tablet dosage. They were paid an additional professional fee per tablet split. Claims submitted from January 2000 through September 2000, involving 14 520 patients, were used to determine the drug costs. This was based on total costs (total prescription costs including supplemental pharmacists’ fee) and per-member-per-month (PMPM) cost.

The total spending for sertraline was a negative slope, meaning the cost decreased with tablet splitting, but this was statistically insignificant. The PMPM cost was however significantly reduced for sertraline in comparison to other SSRIs. In addition, the program did not result in disproportionate numbers of patients changing from sertraline to other SSRIs. Therefore, tablet splitting was considered a cost-effective strategy in the short-term. It was however acknowledged that due to the limitations of this retrospective analysis, no information is available on corresponding physician and hospital claims and how this could influence overall cost.7

Stability, weight and dosage uniformity of split tablets
When tablets are split, it is important to take the stability of the tablet into consideration. For example, some medications may decompose quickly on exposure to air or moisture.6 When tablets are removed from foil packaging and split, the exposed uncoated surface may affect the rate of degradation of active drug, sometimes increasing it. The dissolution and absorption can also be affected; therefore the patient may end up with a lower dose than initially intended.2

In 2002, a study was done on 11 commonly split tablets to determine the dose content of split tablets. This was based on a modified United States Pharmacopeia (USP) Uniformity of Dosage Units test for whole tablets. The USP test for whole tablets allows a Relative Standard Deviation (RSD) of 6%. However, in this modified test for split tablets, 10% was the maximum allowed. In addition, tablet weight was used to...
determine if drug content was equal between the split fractions, as opposed to performing a chemical assay of the actual drug.

The tablets were split using a single-edged razor blade and this was done by a trained individual. The results showed that only three out of the 11 products passed the dose uniformity test, i.e. the respective weights of tablet halves fell within the 85–115% range of calculated average weight and the RSD for each tablet type was less than 10%.4

In 2003, a follow up study was done on 12 products, four of which were similar to the 2002 study.4,13 This time, the products were split using a tablet splitter, but it was also done by a trained pharmacy student. Overall, eight out of the 12 products passed the modified USP Uniformity of Dosage Units test.13

The four products with the same active ingredients as those in the 2002 study were: 4,13

- Lipitor® 40 mg (2002 and 2003) – atorvastatin
- Zestril® 40 mg (2002); Prinivil 40mg (2003) – lisinopril
- Paxil® 40 mg (2002 and 2003) – paroxetine
- Zoloft® 100 mg (2002 and 2003) – sertraline

The comparative results of these four products, together with their physical characteristics are presented in Table I.

It can be seen from Table I that the antidepressants (sertraline and paroxetine) passed the uniformity test in both studies. Their RSDs were lower in the 2003 study when tablets were split by a tablet splitter; the results were actually in line with the required RSD for whole tablets. Lisinopril and atorvastatin however showed contradicting results between the two studies. Interestingly, no visible tablet characteristics (e.g. scoring, shape) determined whether a product would pass or fail the uniformity test.4,13,16

Earlier this year, Hill and colleagues did yet another study to determine the drug content uniformity in split tablets, using drug assay. It was found that 23.9% of half tablets assessed fell outside the proxy USP specifications for drug content. In this case, 22.2% of scored tablets also failed the drug content uniformity test, as opposed to 25.6% of unscored tablets.16

Refer to Table II for individual drug results.

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**Table I: Results of the adapted USP Uniformity of Dosage Units tests for four commonly split tablets1,13**

<table>
<thead>
<tr>
<th>Product and strength per whole tablet</th>
<th>Year: 2002/2003</th>
<th>% Beyond 85–115% and beyond 75–125% of average calculated weight</th>
<th>% RSD</th>
<th>Scored</th>
<th>Oval</th>
<th>Flat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoloft® 100 mg</td>
<td>2002</td>
<td>0 and 0</td>
<td>7.5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Zoloft® 100 mg</td>
<td>2003</td>
<td>0 and 0</td>
<td>3.3</td>
<td>Yes</td>
<td>No (Oblong)</td>
<td>No</td>
</tr>
<tr>
<td>Paxil® 40 mg</td>
<td>2002</td>
<td>0 and 0</td>
<td>4.9</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Paxil® 40 mg</td>
<td>2003</td>
<td>0 and 0</td>
<td>3.5</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Zestril® 40 mg</td>
<td>2002</td>
<td>0 and 0</td>
<td>8.4</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prinivil® 40 mg*</td>
<td>2003</td>
<td>20 and 0</td>
<td>13.4</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lipitor® 40 mg*</td>
<td>2002</td>
<td>25 and 5</td>
<td>12.3</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Lipitor® 40 mg</td>
<td>2003</td>
<td>0 and 0</td>
<td>5.5</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*Products that failed the test

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**Table II: Results of the half tablet drug content uniformity test, as performed by chemical assay16**

<table>
<thead>
<tr>
<th>Drug and strength per whole tablet</th>
<th>Scored</th>
<th>% Beyond proxy USP specification</th>
<th>% Beyond proxy USP specification (weight adjusted)</th>
<th>% RSD</th>
<th>% RSD (weight adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram 40 mg</td>
<td>Yes</td>
<td>16.7</td>
<td>3.3</td>
<td>4.50</td>
<td>3.18</td>
</tr>
<tr>
<td>Simvastatin 80 mg</td>
<td>No</td>
<td>10.0</td>
<td>0</td>
<td>4.29</td>
<td>3.45</td>
</tr>
<tr>
<td>Lisinopril 40 mg</td>
<td>No</td>
<td>33.3</td>
<td>3.33</td>
<td>10.41</td>
<td>8.07</td>
</tr>
<tr>
<td>Metoprolol tartrate 25 mg</td>
<td>Yes</td>
<td>13.3</td>
<td>0</td>
<td>4.73</td>
<td>5.26</td>
</tr>
<tr>
<td>Metoprolol succinate 200 mg</td>
<td>No</td>
<td>33.3</td>
<td>0</td>
<td>8.98</td>
<td>7.67</td>
</tr>
<tr>
<td>Warfarin sodium 5 mg</td>
<td>Yes</td>
<td>36.7</td>
<td>10.0</td>
<td>5.05</td>
<td>4.64</td>
</tr>
</tbody>
</table>

1 % USP range for Warfarin = 95–105%, and for all other products = 90–110%. Note: USP specification ranges used in this study were stricter, as applied to samples of ≥ 20 tablets. The range for individual tablets is usually 85–115%
It was concluded that the weight deviation, resulting from tablets powdering or fragmenting during the splitting process, contributes to the drug content deviation in half tablets. Therefore, the patients’ ability to split tablets in half accurately will determine if daily doses are equal.16

Product characteristics
Scored tablets are usually regarded by the manufacturer to be suitable for splitting.7 The FDA and the PSSA also suggest that tablets which are scored may be safe to split, but that dividing unscored tablets is considered ‘off label’ because of dose irregularities that may arise after splitting the tablet.8,12 However, as demonstrated above and in other reviews, not all scored tablets are split accurately.2,3,4,13

Tablets containing drugs with a long half-life and a wide therapeutic index are considered more appropriate to split. These mostly include tablets used for chronic conditions such as depression, hypertension and hypercholesterolaemia.2,8,14,15 Furthermore, tablets containing drugs with low toxicity and relative flat dose-response relationships may also be suitable for splitting.3,4,15

On the other hand, the dosage fluctuations that occur after tablet splitting may be problematic for drugs with a narrow therapeutic range, such as digoxin and warfarin, because any fluctuation can be detrimental to a patient’s health.2,6 Drugs with a narrow therapeutic index should only be divided if the physiochemical properties are satisfactory and if the most favorable clinical response depends on the lowest available strength being halved.5

Sustained or extended-release tablets are generally not considered appropriate for tablet splitting.2,5,6,8 However, Marriot and Nation report that there are sustained release products that can be split without affecting the release characteristics, for example isosorbide mononitrate and bupropion.2 Isosorbide mononitrate (extended release) is available in three products in South Africa; the package inserts of the controlled release Imdur® and Monicor SR® confirm the above statement that it can be broken in half, but the Elantan LA® product summary states that the tablet should be swallowed whole. The bupropion (Wellbutrin SR®) package insert also states that the tablet should be taken whole and cannot be split.17 It follows that it is vital to consult the product information summary or manufacturer of each specific brand if dividing tablets is considered.2,12

Tablets that have a coating to mask the taste may not be suitable for splitting because the taste can be unmasked.2 Table III provides a basic guide as to which tablets may not be appropriate for splitting.

A tool for evaluation of the appropriateness of tablet splitting, taking product characteristics into account, is presented in Diagram 1.

Patient characteristics
Tablet splitting can be difficult for certain patients and therefore should not be recommended for everyone.6,15 Splitting tablets by hand can be extremely challenging for the elderly.2,10,11 The elderly and children are the group of patients that usually require lower doses of most medications. Chronically ill and elderly patients like those who have Parkinson’s disease and arthritis can find splitting tablets difficult because of impaired grip strength or impaired dexterity.2,6,10

Patients should also be assessed thoroughly for other physical barriers like visual and cognitive impairment before tablet splitting can be implemented.3,5,6,8,14,15

Diagram 2 depicts the patient characteristics that should be considered when evaluating the appropriateness of tablet splitting.

Clinical outcomes
Few studies have measured the effects of splitting tablets on clinical outcomes.16,18 One of the earlier studies consisted of 29 patients taking lisinopril; this was a randomised crossover trial. The two groups of patients took whole lisinopril tablets for two weeks and split tablets for another two weeks. There was no major difference in blood pressure between patients taking whole versus those taking split tablets. However, limitations of the study include a small sample size and short duration of each treatment arm.14

The Veterans Affairs Palo Alto Health Care System tablet splitting program reviewed the effects of tablet splitting of

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**Table III: Types of tablets unsuitable for splitting**2,3,5,6,8,12

<table>
<thead>
<tr>
<th>Types of tablets that should not be split</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Film-coated tablets</td>
<td>Donezepil, tamoxifen, nifedipine, azathioprine</td>
</tr>
<tr>
<td>Time-release and extended-release tablets</td>
<td>Potassium chloride, cefaclor CD, tramadol SR</td>
</tr>
<tr>
<td>Enteric-coated tablets</td>
<td>Mesalazine, valproate, pantoprazole, dipyridamole</td>
</tr>
<tr>
<td>Unscored tablets</td>
<td>Metformin 850 mg, acarbose 50 mg, d-penicillamine</td>
</tr>
<tr>
<td>Thick or oddly shaped tablets</td>
<td>Fosinapril, amiloride, alendronate, fainemester 5 mg, lamotrigine</td>
</tr>
<tr>
<td>Small size</td>
<td>Digoxin, temazepam</td>
</tr>
</tbody>
</table>
Diagram 1: Tablet characteristics to consider for tablet splitting \(^{2,3,8,11,15}\)

- **Is tablet scored?**
  - **YES**: Splitting may be appropriate. Patient characteristics must be considered.
  - **NO**
    - **Is tablet a controlled or extended-release formulation?**
      - **YES**: Tablet should not be split.
      - **NO**
        - **Is tablet a combined formulation?**
          - **YES**: Tablet should not be split.
          - **NO**
            - **Does tablet have a narrow therapeutic window?**
              - **YES**: Splitting may not be appropriate. Patient characteristics must be considered.
              - **NO**
                - **Is tablet film-coated or coated to mask taste?**
                  - **YES**: Splitting may not be appropriate. Patient characteristics must be considered.
                  - **NO**
                    - **Is tablet difficult to split? (Small size or irregular shape)**
                      - **YES**: Splitting may not be appropriate. Patient characteristics must be considered.
                      - **NO**: Splitting may be appropriate. Patient characteristics must be considered.
simvastatin, lovastatin and atorvastatin on lipid profiles. Laboratory analysis was conducted on 512 patients. The lipid profile was taken between one year before and the day tablet splitting was initiated, this period was called the prelab. The postlab lipid profile was taken between six weeks and one year after initiation of tablet splitting. In this study, there was no major difference between preintervention and postintervention in laboratory values of total cholesterol and triglycerides. There was however, a statistically significant decrease in LDL and an increase in HDL, which was attributed to intake of whole tablets, as well as lifestyle and diet modifications. No significant adverse events, including rhabdomyolysis, were identified after tablet splitting was implemented.8,14

A study was also done to evaluate clinical outcomes on splitting risperidone tablets in schizophrenic patients. This is the group of patients who are often recommended to be excluded from any tablet splitting program because of possible cognitive impairment. The study was a retrospective analysis of administrative data from one region of the Veterans Health Administration for 2346 schizophrenic individuals who were prescribed risperidone from January 2001 to March 2003. Risperidone tablets were chosen because they are scored and easy to split, and the price of higher strengths is similar to that of lower strengths. The study end points were as follows:

- Medication adherence, using the medication possession ratio (MPR). The MPR is the number of days' supply of risperidone actually dispensed divided by the number of days the patient is expected to be on medication. An MPR of 1.0 would indicate that, on average, the patient obtained refills on time.
- Clinical stability, as measured by outpatient service utilisation.
- Clinical outcomes, as measured by inpatient admission rates.

It was found that the MPR increased after initiating tablet splitting; it increased from 0.83 presplitting to 0.90 post-splitting (p < 0.001). Unscheduled appointments in an outpatient facility increased from 0.08 to 0.32 (p < 0.001), especially in the first two months, and the ratio of unscheduled to scheduled appointments kept also increased significantly from 0.08 to 0.54 (p < 0.001). The increased MPRs and unscheduled visits suggest that some patients may have

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Diagram 2: Patient characteristics to consider for tablet splitting8,8,11

- Is tablet-splitting required for titration of dose/Strength is unavailable?
  - NO
  - YES
    - Does patient have many tablets to split/complicated regimen?
      - NO
        - YES
          - Does patient have any physical/cognitive difficulties (impaired grip strength, visual acuity; age)?
            - NO
              - YES
                - Splitting is appropriate. Patient must be counselled on tablet splitting.
            - YES
              - Splitting may be inappropriate. Additional compliance measures must be considered.
          - YES
            - Splitting may be inappropriate. Dispensing a different dosage form must be considered.
    - YES
      - Splitting may be inappropriate. Additional compliance measures must be considered.

Tablet should not be split
experienced some difficulty in the first few weeks after tablet division was introduced. The difficulties could have been related to tablets crumbling, mechanical problems or misinterpretation of splitting instructions. There was however no major change in scheduled visits, psychiatric hospital admission or any general admissions. It can therefore be concluded from this study that tablet splitting was followed by an increase in outpatient utilisation, but had no clear impact on clinical outcomes.18

Patient satisfaction
The investigators of the 2002 modified USP uniformity test stated that, given the public’s expectations for high product standards, advocating the division of higher strength tablets to reduce costs would be a compromise of community principles, rather than a practice right.4 However, it was acknowledged that the public may choose to trade money savings for lower health standards and that they should be consulted in order to establish acceptable standards.4,13

Indeed, in another study 89% and 97% of patients stated that they would split tablets to save costs for themselves, or their health scheme, respectively.4 In the statin tablet splitting study, the majority of patients were satisfied and compliant with the program. Notably, 74% agreed that dividing tablets was not too time-consuming or bothersome, but 46% thought it was easier to take medications when they did not have to split the tablet.14 Other studies also showed that tablet splitting is well accepted by patients and does not have a negative effect on compliance.2,13,14

Errors that can occur with tablet splitting
• A prescription written as ½ tablet can be read by the pharmacist as 1–2 tablets, and this can lead to overdose. The prescriber should rather write the strength that is required in milligrams.1,6
• Healthcare providers can issue the wrong formulations for splitting, for example enteric-coated or sustained-release tablets.4
• Patients often do not read the labels correctly. It is important for pharmacists to counsel patients adequately and ensure that the instructions on the label are understood.1,2,5
• Patients may forget to split tablets. They may take a whole tablet assuming the tablet has been split before dispensing, or based on the doctor’s original verbal instruction of “Take one tablet”.1,5,6
• Patients may split tablets again without remembering or realising that they have been split by the pharmacist or pharmacist’s assistant already. They may even get confused and split the wrong product.1,6
• The patient can also stop taking medication due to laziness to split the tablet.1,6
• Promoting the concept of half tablets could encourage some patients to split other tablets that should always be taken whole.11

Conclusion
Tablet splitting can certainly not be recommended for all products just to reduce the costs.2,3,6 The reduction of cost achieved by splitting tablets is noteworthy, but not always appropriate as there are quite a number of factors to be considered even if the product is scored.2,4,11 Prescribers and pharmacists should be considerate of tablet formulation and patient characteristics before implementing tablet splitting.2,6,11 When implemented appropriately and carefully, tablet splitting does not appear to significantly affect clinical and humanistic outcomes.2,14,16,18 Patients should however be counselled adequately in order to avoid over- or under-dosing.1,5,11

References: